

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 2

II. AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method for alkylating a glycopeptide that comprises a saccharide-amine; the method comprising:
 - (a) combining an aldehyde or ketone, a suitable base, and the glycopeptide or a salt thereof, to provide a reaction mixture;
 - (b) acidifying the reaction mixture; and
 - (c) combining the reaction mixture with a suitable reducing agent, to provide a glycopeptide that is alkylated at the saccharide-amine.
2. (Original) The method of claim 1 wherein the glycopeptide comprises at least one amino group other than the saccharide-amine.
3. (Original) The method of claim 2 wherein reductive alkylation at the saccharide-amine is favored over reductive alkylation at the other amino group of the glycopeptide by at least about 10:1.
4. (Original) The method of claim 2 wherein reductive alkylation at the saccharide-amine is favored over reductive alkylation at the other amino group of the glycopeptide by at least about 20:1.
5. (Currently Amended) The method of claim 1 wherein the reductive alkylation is carried out in the presence of a suitable solvent.
6. (Currently Amended) The method of claim 5 wherein the solvent is a halogenated hydrocarbon, a linear or branched ether, an aromatic hydrocarbon, an alcohol, dimethylsulfoxide, N,N-dimethylformamide, acetonitrile, water, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone, tetramethyl urea, N,N-dimethylacetamide, diethylformamide, 1-methyl-2-pyrrolidinone, tetramethylenesulfoxide, glycerol, ethyl acetate, isopropyl acetate, N,N-dimethylpropylene urea,

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 3

or dioxane, or a mixture thereof.

7. (Currently Amended) The method of claim 6 wherein the solvent is acetonitrile, water, DMF N,N-dimethylformamide, or methanol, or mixtures thereof.

8. (Original) The method of claim 1 wherein the reaction mixture that is combined with the reducing agent comprises a protic solvent.

9. (Original) The method of claim 1 wherein the reductive alkylation is carried out at a temperature in a range of about 0 °C to about 50 °C.

10. (Original) The method of claim 1 wherein the base is a tertiary amine.

11. (Currently Amended) The method of claim 1 wherein the acid is reaction mixture is acidified with a carboxylic acid or a mineral acid.

12. (Currently Amended) The method of claim 1 wherein the acid is reaction mixture is acidified with trifluoroacetic acid.

13. (Original) The method of claim 1 wherein the reducing agent is sodium cyanoborohydride, sodium triacetoxyborohydride, pyridine/borane, sodium borohydride, or zinc borohydride.

14. (Original) The method of claim 1 wherein the reducing agent is a hydrogen source and a transition metal catalyst.

U.S. Serial No. 09/847,060
 Attorney Docket No. P-090-US1
 Customer Number 27038

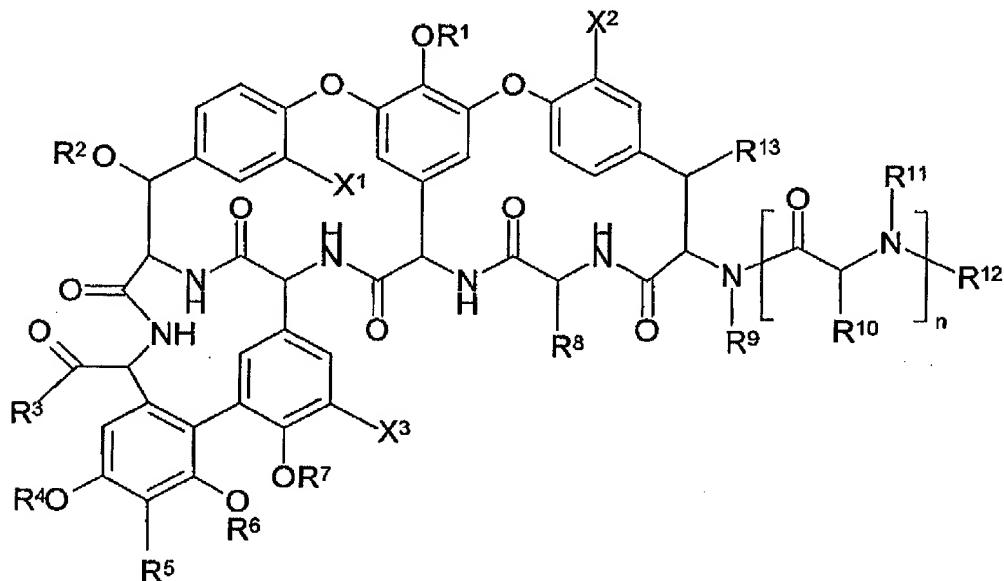
Page 4

15. (Currently Amended) ~~The A method of claim 1 further comprising for preparing an alkylated glycopeptide, the method comprising:~~

- (a) ~~combining an aldehyde or ketone, a base, and a glycopeptide or a salt thereof, to provide a reaction mixture;~~
- (b) ~~acidifying the reaction mixture;~~
- (c) ~~combining the reaction mixture with a reducing agent to provide a glycopeptide that is alkylated at the saccharide-amine; and~~
- (d) isolating the alkylated glycopeptide.

16. (Currently Amended) A method for preparing an alkylated glycopeptide, ~~the method comprising:~~

- (a) combining an aldehyde or ketone, a suitable base, and a compound of formula I:



(I)

wherein:

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 5

R¹ is an amino saccharide group;

R² is hydrogen or a saccharide group;

R³ is R³-is -OR^c, -NR^cR^c, -O-R^a-Y-R^b-(Z)_x, -NR^c-R^a-Y-R^b-(Z)_x, -NR^cR^c, or -O-R^c;

R⁴ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, -C(O)R^d and a saccharide group;

R⁵ is selected from the group consisting of hydrogen, halo, -CH(R^c)-NR^cR^c, -CH(R^c)-NR^cR^e, -CH(R^c)-NR^c-R^a-Y-R^b-(Z)_x, -CH(R^c)-R^x, and -CH(R^c)-NR^c-R^a-C(=O)-R^x;

R⁶ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, -C(O)R^d and a saccharide group;

R⁷ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, and -C(O)R^d;

R⁸ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R⁹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R¹⁰ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; or R⁸ and R¹⁰ are joined to form -Ar¹-O-Ar²-, where Ar¹ and Ar² are independently arylene or heteroarylene;

R¹¹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic, or R¹⁰ and R¹¹ are joined, together with the carbon and nitrogen atoms to which they are attached, to form a heterocyclic ring;

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 6

R^{12} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, $-C(O)R^d$, $-C(NH)R^d$, $-C(O)NR^cR^c$, $-C(O)OR^d$, and $-C(NH)NR^cR^c$, or R^{11} and R^{12} are joined, together with the nitrogen atom to which they are attached, to form a heterocyclic ring;

R^{13} is selected from the group consisting of hydrogen or $-OR^{14}$;

R^{14} is selected from hydrogen, $-C(O)R^d$ and a saccharide group;

each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-C(O)R^d$;

each R^d is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^e is a saccharide group;

R^x is a nitrogen-linked amino saccharide or a nitrogen-linked heterocycle;

X^1 , X^2 and X^3 are independently selected from hydrogen or chloro;

each Y is independently selected from the group consisting of oxygen, sulfur, $-S-S-$, $-NR^c-$, $-S(O)-$, $-SO_2-$, $-NR^cC(O)-$, $-OSO_2-$, $-OC(O)-$, $-NR^cSO_2-$, $-C(O)NR^c-$, $-C(O)O-$, $-SO_2NR^c-$, $-SO_2O-$, $-P(O)(OR^c)O-$, $-P(O)(OR^c)NR^c-$, $-OP(O)(OR^c)O-$, $-OP(O)(OR^c)NR^c-$, $-OC(O)O-$, $-NR^cC(O)O-$, $-NR^cC(O)NR^c-$, $-OC(O)NR^c-$, $-C(=O)-$, and $-NR^cSO_2NR^c-$;

each Z is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl

U.S. Serial No. 09/847,060
 Attorney Docket No. P-090-US1
 Customer Number 27038
 Page 7

and heterocyclic;

n is 0, 1 or 2; and

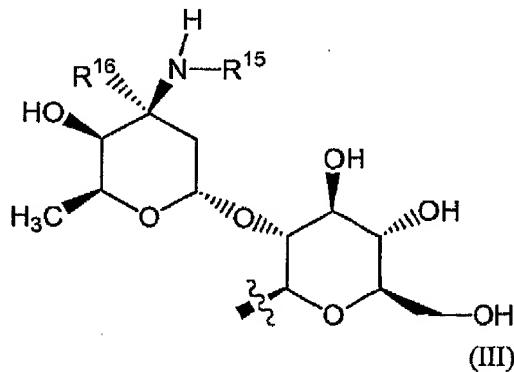
x is 1 or 2;

or a stereoisomer or salt thereof; to provide a reaction mixture;

(b) acidifying the reaction mixture; and

(c) combining the reaction mixture with a suitable reducing agent, to provide the corresponding glycopeptide alkylated at the amino group of the amino saccharide.

17. (Original) The method of claim 16 wherein R¹ is an amino saccharide of formula (III):



wherein R¹⁵ is H; and R¹⁶ is hydrogen or methyl.

18. (Original) The method of claim 16 wherein R², R⁴, R⁶, and R⁷ are each hydrogen.

19. (Original) The method of claim 16 wherein R³ is -OH.

20. (Original) The method of claim 16 wherein R⁵ is hydrogen, -CH₂-NHR^c, -CH₂-NR^cR^c or -CH₂-NH-R^a-Y-R^b-(Z)_x.

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 8

21. (Original) The method of claim 16 wherein the alkylated glycopeptide is a compound of formula I wherein R¹ is an amino saccharide wherein the saccharide-amine is substituted with -R^a-Y-R^b-(Z)_x, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, or substituted cycloalkenyl.

22. (Original) The method of claim 16 wherein the alkylated glycopeptide is a compound of formula I wherein R¹ is an amino saccharide wherein the saccharide-amine is substituted with -CH₂CH₂-NH-(CH₂)₉CH₃; -CH₂CH₂CH₂-NH-(CH₂)₈CH₃; -CH₂CH₂CH₂CH₂-NH-(CH₂)₇CH₃; -CH₂CH₂-NHSO₂-(CH₂)₉CH₃; -CH₂CH₂-NHSO₂-(CH₂)₁₁CH₃; -CH₂CH₂-S-(CH₂)₈CH₃; -CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₁₀CH₃; -CH₂CH₂CH₂-S-(CH₂)₈CH₃; -CH₂CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂CH₂-S-(CH₂)₃-CH=CH-(CH₂)₄CH₃ (*trans*); -CH₂CH₂CH₂CH₂-S-(CH₂)₇CH₃; -CH₂CH₂-S(O)-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₆Ph; -CH₂CH₂-S-(CH₂)₈Ph; -CH₂CH₂CH₂-S-(CH₂)₈Ph; -CH₂CH₂-NH-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂-NH-CH₂-4-[4-(CH₃)₂CHCH₂]-Ph; -CH₂CH₂-NH-CH₂-4-(4-CF₃-Ph)-Ph; -CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-S-CH₂-4-[3,4-di-Cl-PhCH₂O-]-Ph; -CH₂CH₂-NHSO₂-CH₂-4-[4-(4-Ph)-Ph]-Ph; -CH₂CH₂CH₂-NHSO₂-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-NHSO₂-CH₂-4-(Ph-C≡C-)-Ph; -CH₂CH₂CH₂-NHSO₂-4-(4-Cl-Ph)-Ph; or -CH₂CH₂CH₂-NHSO₂-4-(naphth-2-yl)-Ph.

23. (Original) The method of claim 17 wherein the alkylated glycopeptide is a compound of formula I wherein R¹ is a saccharide group of formula III, wherein R¹⁵ is -R^a-Y-R^b-(Z)_x, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl.

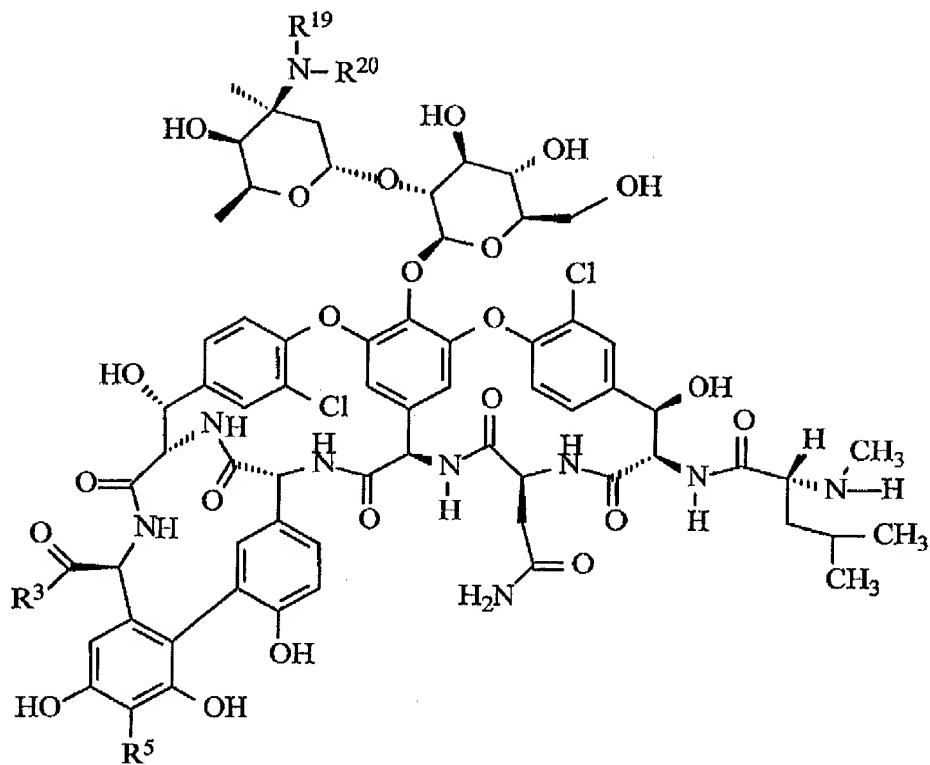
U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 9

24. (Original) The method of claim 23 wherein R¹⁵ is -CH₂CH₂-NH-(CH₂)₉CH₃;
-CH₂CH₂CH₂-NH-(CH₂)₈CH₃; -CH₂CH₂CH₂CH₂-NH-(CH₂)₇CH₃;
-CH₂CH₂-NHSO₂-(CH₂)₉CH₃; -CH₂CH₂-NHSO₂-(CH₂)₁₁CH₃; -CH₂CH₂-S-(CH₂)₈CH₃;
-CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₁₀CH₃; -CH₂CH₂CH₂-S-(CH₂)₈CH₃;
-CH₂CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂CH₂-S-(CH₂)₃-CH=CH-(CH₂)₄CH₃ (*trans*);
-CH₂CH₂CH₂CH₂-S-(CH₂)₇CH₃; -CH₂CH₂-S(O)-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₆Ph;
-CH₂CH₂-S-(CH₂)₈Ph; -CH₂CH₂CH₂-S-(CH₂)₈Ph; -CH₂CH₂-NH-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂-NH-CH₂-4-[4-(CH₃)₂CHCH₂-]-Ph; -CH₂CH₂-NH-CH₂-4-(4-CF₃-Ph)-Ph;
-CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂CH₂-S-CH₂-4-[3,4-di-Cl-PhCH₂O-]-Ph; -CH₂CH₂-NHSO₂-CH₂-4-[4-(4-Ph)-Ph]-Ph;
-CH₂CH₂CH₂-NHSO₂-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-NHSO₂-CH₂-4-(Ph-C≡C-)-Ph;
-CH₂CH₂CH₂-NHSO₂-4-(4-Cl-Ph)-Ph; or -CH₂CH₂CH₂-NHSO₂-4-(naphth-2-yl)-Ph.

25. (Currently Amended) A method for preparing an alkylated glycopeptide, the method comprising:

(a) combining an aldehyde or ketone, a suitable base, and a compound of formula II:

U.S. Serial No. 09/847,060
 Attorney Docket No. P-090-US1
 Customer Number 27038
 Page 10



wherein:

R^3 is $-OR^c$, $-NR^cR^c$, $-O-R^a-Y-R^b-(Z)_x$, $-NR^c-R^a-Y-R^b-(Z)_x$, $-NR^cR^e$, or $-O-R^e$;

R^5 is selected from the group consisting of hydrogen, halo, $-CH(R^c)-NR^cR^c$, $-CH(R^c)-NR^eR^e$, and $-CH(R^c)-NR^c-R^a-Y-R^b-(Z)$;

R^{19} and R^{20} are each hydrogen;

each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

U.S. Serial No. 09/847,060
 Attorney Docket No. P-090-US1
 Customer Number 27038
 Page 11

each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and -C(O)R^d;

R^e is a saccharide group;

each Y is independently selected from the group consisting of oxygen, sulfur, -S-S-, -NR^c-, -S(O)-, -SO₂-, -NR^cC(O)-, -OSO₂-, -OC(O)-, -NR^cSO₂-, -C(O)NR^c-, -C(O)O-, -SO₂NR^c-, -SO₂O-, -P(O)(OR^c)O-, -P(O)(OR^c)NR^c-, -OP(O)(OR^c)O-, -OP(O)(OR^c)NR^c-, -OC(O)O-, -NR^cC(O)O-, -NR^cC(O)NR^c-, -OC(O)NR^c- and -NR^cSO₂NR^c-;

each Z is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic; and

x is 1 or 2; or a stereoisomer or salt thereof; to provide a reaction mixture;

(b) acidifying the reaction mixture; and

(c) combining the reaction mixture with a suitable reducing agent, to provide the corresponding alkylated glycopeptide wherein R²⁰ is -R^a-Y-R^b-(Z)_x, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, or substituted cycloalkenyl.

26. (Original) The method of claim 25 wherein R²⁰ is -CH₂CH₂-NH-(CH₂)₉CH₃; -CH₂CH₂CH₂-NH-(CH₂)₈CH₃; -CH₂CH₂CH₂CH₂-NH-(CH₂)₇CH₃; -CH₂CH₂-NHSO₂-(CH₂)₉CH₃; -CH₂CH₂-NHSO₂-(CH₂)₁₁CH₃; -CH₂CH₂-S-(CH₂)₈CH₃; -CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₁₀CH₃; -CH₂CH₂CH₂-S-(CH₂)₈CH₃; -CH₂CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂CH₂-S-(CH₂)₃-CH=CH-(CH₂)₄CH₃ (*trans*); -CH₂CH₂CH₂CH₂-S-(CH₂)₇CH₃; -CH₂CH₂-S(O)-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₆Ph; -CH₂CH₂-S-(CH₂)₈Ph; -CH₂CH₂CH₂-S-(CH₂)₈Ph; -CH₂CH₂-NH-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂-NH-CH₂-4-[4-(CH₃)₂CHCH₂]-Ph; -CH₂CH₂-NH-CH₂-4-(4-CF₃-Ph)-Ph; -CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph;

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 12

-CH₂CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂CH₂-S-CH₂-4-[3,4-di-Cl-PhCH₂O-)-Ph; -CH₂CH₂-NHSO₂-CH₂-4-[4-(4-Ph)-Ph]-Ph;
-CH₂CH₂CH₂-NHSO₂-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-NHSO₂-CH₂-4-(Ph-C≡C-)-Ph;
-CH₂CH₂CH₂-NHSO₂-4-(4-Cl-Ph)-Ph; or -CH₂CH₂CH₂-NHSO₂-4-(naphth-2-yl)-Ph.

27. (Original) The method of claim 1, further comprising preparing a pharmaceutically acceptable salt of the alkylated glycopeptide.

28. (Original) The method of claim 1, further comprising, combining a pharmaceutically acceptable carrier with the alkylated glycopeptide to provide a pharmaceutical composition.

29. (Original) The method of claim 27, further comprising, combining a pharmaceutically acceptable carrier with the salt, to provide a pharmaceutical composition.

30. (New) A process for preparing an alkylated glycopeptide, the process comprising the steps of:

- (a) contacting a glycopeptide having a amino-containing saccharide group with an aldehyde or ketone in the presence of a tertiary amine to form a reaction mixture;
- (b) acidifying the reaction mixture from step (a) with an acid;
- (c) contacting the reaction mixture from step (b) with a reducing agent to form an alkylated glycopeptide.

31. (New) The process of claim 30, wherein the glycopeptide is vancomycin or A82846B.

32. (New) The process of claim 30, wherein the tertiary amine is diisopropylethylamine, N-methylmorpholine or triethylamine.

U.S. Serial No. 09/847,060
Attorney Docket No. P-090-US1
Customer Number 27038
Page 13

33. (New) The process of claim 30, wherein the acid is trifluoroacetic acid.
34. (New) The process of claim 30, wherein the reducing agent is sodium cyanoborohydride, sodium triacetoxyborohydride, pyridine/borane, sodium borohydride or zinc borohydride.